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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,706	03/14/2001	William A. McMillan	22660-0025 DIV 2	6375
7590 11/19/2003			EXAMINER	
Townsend and Townsend and, LLP Two Embarcadero Center Eighth Floor San Francisco, CA 94111-3834			SWITZER, JULIET CAROLINE	
			ART UNIT	PAPER NUMBER
			1634	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/808,706

Applicant(s)

MCMILLAN ET AL.

Examiner

Juliet C. Switzer

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-- **Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --**
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 and 29-51 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 and 29-51 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 14 March 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☒ Interview Summary (PTO-413) Paper No(s). 1103.
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. 6) ☐ Other: _____

DETAILED ACTION

1. This office action is written in response to applicant's correspondence that was received 8/15/03, a faxed copy of which was also received 9/10/03. Applicant amended claim 1, cancelled claims 9-28, and added claims 29-51. Claims 1-8 and 29-51 are pending and examined herein.

2. The previous rejection set forth under 103 is hereby withdrawn in view of applicant's arguments provided on pages 10-13 of the response. New grounds of rejection are set forth. This action is non-final.

3. The abstract of the disclosure is objected to because it contains more than 150 words. Correction is required. See MPEP 608.01(b).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 37 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In claims 37 and 48 the new method limitations wherein the minimum of the second order curve (that is fit to the second derivative data points) is determined using a ratio of determinants appears to be new matter.

No specific basis for these limitations was identified in the specification, nor did a review of the specification by the examiner find any basis for the limitations. The specification teaches using a peak finding algorithm that determines the height of the peak of a second order curve and the cycle number of the peak using a ratio of four determinants (p. 88, lines 11-29). However, the specification does not appear to teach a method which uses a ratio of determinants to determine the minimum of a second order curve, as is recited in instant claims 37 and 48. The remarks filed with this amendment do not identify basis for the new claim limitation.

Since no basis has been identified by applicant or by the examiner, the claims are rejected as incorporating new matter.

6. Claims 35, 37, 39, 46, 48, and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 35, 39, 46, and 50 are drawn to a method for quantifying target nucleic acid, and recite a step of using a ratio of determinants to determine the peak of a second order curve.

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Claims 37 and 48 are also drawn to a method of quantifying target nucleic acid, and these recite a step of using a ratio of determinants to calculate the minimum of a second order curve.

The specification teaches a method wherein a particular set of determinants are calculated based on the x,y values of three data points, and then a particular set of ratios are used to calculate the maximum of a second order curve (see specification page 88, lines 11-29, and the determinants and ratios given in Figure 31). The claims embrace the use of any possible ratios of determinants to calculate a maximum or a minimum of a second order curve. The specification only provides a single example of such ratios and the determinants used to calculate them, and does not further describe any other possible ratios of determinants that can be used to calculate the maximum of a second order curve. The specification does not describe any possible ratios of determinants that can be used to calculate the minimum of a second order curve, as is recited in claims 37 and 48. There is no apparent commonality for the matrices whose determinants would be useful to determine the characteristics of the curve, or other determinants whose ratios would be useful to determine peak maximums or minima. Due to the breadth of the claims, with regard to the fact that only a single possible set of determinants and ratios thereof are given in the specification, the claims are rejected for lack of written description because the claims embrace the use of a wide variety of determinants and ratios thereof for which no written description is provided.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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8. Claims 30-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 30-51 recites the limitation "the apparatus of claim 29" in the preamble of the claims, yet claim 29 is drawn to a method. Additionally, the limitations that follow the preamble of claims 30-51 appear to be method limitations, and so it is confusing as to whether applicant intended to refer back to an apparatus (and if so what apparatus) or the method of claim 29. There is insufficient antecedent basis for this limitation in the claim. In light of the interview with applicant's attorney (11/11/03), the claims will be interpreted as meaning to further limit the method of claim 29.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-8, 29-34, 36, 38, 40-45, 47, 49, and 51 are rejected under 35 U.S.C. 102(e) as being anticipated by Wittwer *et al.* (US 6303305).

Wittwer *et al.* teach a method for determining an unknown starting quantity of a target nucleic acid sequence in a test sample, the method comprising the steps of:

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(a) amplifying the unknown starting quantity of the target nucleic acid sequence in the test sample (Col. 4, lines 13-16; Col. 7, lines 47-48);

(b) amplifying a plurality of known starting quantities of a calibration nucleic acid sequence in respective calibration samples (Col. 7, lines 48-50);

(c) determining a respective threshold value for each of the known starting quantities of the calibration nucleic acid sequence in the calibration samples and for the target nucleic acid sequence in the test sample, wherein the threshold value is determined for each nucleic acid sequence in a respective sample by:

(i) measuring at a plurality of times during amplification, at least one signal whose intensity is related to the quantity of the nucleic acid sequence being amplified in the sample (Col. 7, lines 48-50) ;

(ii) deriving a growth curve from the measurements of the signal (Col. 7, line 51);

(iii) calculating a derivative growth curve (Col. 7, lines 51-53);

(iv) identifying a characteristic of the derivative (Col. 7, lines 51-52); and

(v) determining a threshold value (i.e. a cycle number) associated with the characteristic of the derivative (Col. 5, lines 43-67; Col. 7, lines 54-55);

(d) deriving a calibration curve from the threshold values determined for the known starting quantities of the calibration nucleic acid sequence in the calibration samples (Col. 7, lines 44-56); and

(e) determining the starting quantity of the target nucleic acid sequence in the test sample using the calibration curve and the threshold value determined for the target sequence (Col. 7, lines 55-56).

With regard to claim 2, Wittwer *et al.* teach a threshold value that comprises cycle number, that is, Wittwer *et al.* teach that the determination of extrema, such as the maximum or minimum of the second derivative of the curve provides a set point for the definition of the fractional cycle number characteristic for each value, which reflects the initial concentration of the analyte (Col. 5, lines 62-67). That is, the threshold amount of cycles (i.e. time necessary) for a given concentration of sample to produce an observable signal.

With regard to claim 3, Wittwer *et al.* the determination of cycle number is a determination of the elapsed time of amplification, as each cycle of a PCR amplification is a fixed period of time (see for example lines 25-30 of Col. 8) and thus, cycle number is a measure of the time elapsed from the beginning of the PCR.

With regard to claim 4, Wittwer *et al.* teach a step of calculating a derivative of the growth curve that comprises calculating a second derivative of the growth curve, wherein the characteristic comprises a positive peak of the second derivative, referred to therein as the maxima of the derivative (Col. 5, lines 62-65).

With regard to claim 5, Wittwer *et al.* teach a step of calculating a second derivative of the growth curve wherein the characteristic comprises a negative peak of the second derivative, referred to therein as the minimum of the derivative (Col. 5, lines 62-65).

With regard to claim 6, Wittwer *et al.* teach a step of calculating a second derivative of the growth curve wherein the characteristic comprises a zero crossing of the second derivative (Col. 5, lines 62-65).

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With regard to claim 7, Wittwer *et al.* teach a step of calculating a first derivative of the growth curve wherein the characteristic comprises a positive peak of the first derivative (Col. 5, lines 62-65).

With regard to claim 8, Wittwer *et al.* disclose the method wherein the calculation comprises calculating second derivative values of the growth curve at a number of different measurement points in the reaction to yield a plurality of second derivative data points derivative data points, the characteristic comprising a positive peak of the second derivative, and the step of determining the threshold value associated with the positive peak comprising fitting a second order curve to the data point and calculating the threshold value as the location of a peak of the second order curve (Col. 6, lines 1-34, Figure 4).

With regard to claim 29, Wittwer *et al.* teach a method for determining an unknown starting quantity of a target nucleic acid sequence in a test sample, the method comprising the steps of:

(a) amplifying the unknown starting quantity of the target nucleic acid sequence in the test sample (Col. 4, lines 13-16; Col. 7, lines 47-48);

(b) amplifying a plurality of known starting quantities of a calibration nucleic acid sequence in respective calibration samples (Col. 7, lines 48-50);

(c) determining a respective threshold value for each of the known starting quantities of the calibration nucleic acid sequence in the calibration samples and for the target nucleic acid sequence in the test sample, wherein the threshold value is determined for each nucleic acid sequence in a respective sample by:

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(1) measuring at a plurality of times during amplification, at least one signal whose intensity is related to the quantity of the nucleic acid sequence being amplified in the sample (Col. 7, lines 48-50) ;

(2) store signal values defining a growth curve for the nucleic acid sequence, wherein the growth curve expresses signal intensity as a function of cycle number or as a function of time of amplification (via plotting, see Figure 2);

(3) determine a derivative of the growth curve, wherein the derivative is determine with respect to cycle number or time (Col. 7, lines 51-53); and

(4) calculating a threshold cycle number associated with a characteristic of the derivative (Col. 5, lines 43-67; Col. 7, lines 54-55);

(d) deriving a calibration curve from the threshold values determined for the known starting quantities of the calibration nucleic acid sequence in the calibration samples (Col. 7, lines 44-56); and

(e) determining the starting quantity of the target nucleic acid sequence in the test sample using the calibration curve and the threshold value determined for the target sequence (Col. 7, lines 55-56).

With regard to claim 30, Wittwer *et al.* teach a step of determining the second derivative of the growth curve with respect to cycle number and calculating the threshold cycle number as the location, in cycles, of a maximum of the second derivative (Col. 5, lines 62-65; Figure 2; Example 1(B)). With regard to claims 31 and 32, Wittwer *et al.* also teach that the minimum or zero-crossing of the second derivative may be used (Col. 5, lines 62-65). With regard to claim

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33, Wittwer *et al.* additionally teach the use of the maximum of the first derivative (Col. 5, lines 62-65).

With regard to claim 34, Wittwer *et al.* teach steps of calculating second derivative values of the growth curve, with respect to cycle number, at a number of different points to yield a plurality of second derivative data points, fitting a second curve to at least three of the second derivative data points; and calculating a threshold cycle number as the location, in cycles, of a positive peak of the second curve. With regard to claims 36, 38, and 40, Wittwer *et al.* additionally teach that the second curve fitting method can be applied to both first and second derivatives and that extrema that can be determined include, maximum, minimum or zero values (Col. 5, line 62-Col. 6, line 34, Figure 4).

With regard to claim 41, Wittwer *et al.* teach a step of determining the second derivative of the growth curve with respect to cycle number (which is a measure of time of amplification) and calculating the threshold cycle number as the location, in cycles, of a maximum of the second derivative (Col. 5, lines 62-65; Figure 2; Example 1(B)). With regard to claims 42 and 43, Wittwer *et al.* also teach that the minimum or zero-crossing of the second derivative may be used (Col. 5, lines 62-65). With regard to claim 44, Wittwer *et al.* additionally teach the use of the maximum of the first derivative (Col. 5, lines 62-65).

With regard to claim 45, Wittwer *et al.* teach steps of calculating second derivative values of the growth curve, with respect to cycle number, at a number of different points to yield a plurality of second derivative data points, fitting a second curve to at least three of the second derivative data points; and calculating a threshold cycle number as the location, in cycles, of a positive peak of the second curve. With regard to claims 47, 49, and 51, Wittwer *et al.*

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additionally teach that the second curve fitting method can be applied to both first and second derivatives and that extrema that can be determined include, maximum, minimum or zero values (Col. 5, line 62-Col. 6, line 34, Figure 4).

Thus, the teachings of Wittwer *et al.* anticipate each of the rejected claims.

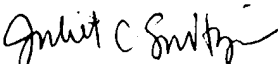
Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


Juliet C Switzer
Examiner
Art Unit 1634

November 16, 2003